REMARKS

This document is submitted in response to the Office Action dated August 8, 2006 ("Office Action").

Applicants have cancelled claim 60. The cancellation of this claim has necessitated change of dependency of claim 62. Upon entry of the present amendments, claims 27, 29, 58, 59, and 62-64 will be under examination.

The Examiner rejects claims 27, 29, 58-60, and 62-64 under 35 U.S.C. § 103 on two grounds. Applicants traverse both grounds separately below.

Rejection over Kamarei in view of Proksch

Claim 27 is rejected as being obvious over Kamarei et al., US Patent 4,749,522 ("Karamei") in view of Proksch et al., US Patent 4,216,117 ("Proksch"). See the Office Action, pages 3-5, section 5. Applicants respectfully disagree.

Claim 27 covers a method of producing a denatured lipoprotein standard. This method includes the following steps: (1) **freezing** a solution containing lipoprotein to produce a frozen solution of lipoprotein, (2) **melting** the frozen solution to produce a melted solution of denatured lipoprotein, (3) **freeze-drying the melted solution** to produce stabilized denatured lipoprotein in powder form, and (4) determining an amount of the denatured lipoproteins in the powder. Clearly, steps (1) and (2), in combination, is a **freeze-melting (freeze-thawing)** step. As step (3) recites **freeze-drying the melted (thawed) solution**, claim 27 clearly requires performing **freeze-thawing first,** i.e., steps (1) and (2), **and then freeze-drying,** i.e., step (3).

Kamarei teaches supercritical fluid extraction of biomaterials (e.g., lipoprotein) from animal tissues (e.g., blood plasma). It discloses **26** methods (e.g., freeze-thawing and freeze-drying) and their combinations that can be used to prepare tissues for supercritical fluid extraction. See column 8, lines 39-52, and page 11, lines 10-22 below.

Proksch teaches "a lipoprotein diluent useful in the preparation of a standard or reference material for assay procedures which comprises a stabilized aqueous solution of turbidity-potential lipoproteins." See Abstract. It discloses two examples of preparing two types of lipoprotein extracts which are useful for standards and references for **cholesterol** and **triglyceride** assays. See

column 8, lines 8-10 and 44-46. It also discloses an example of diluting the lipoprotein extracts thus prepared in varying proportions to obtain solutions of differing concentrations of **cholesterol** and **triglyceride**. See column 9, lines 21-22. In other words, Proksch teaches determining the amounts of **cholesterol** and **triglyceride** in lipoprotein diluents.

The Examiner alleges that it would have been obvious, at the time of the invention, to a person of ordinary skill to practice claim 27 by modifying the teachings in Kamarei in view of Proksch. See the Office Action, page 4, last paragraph. According to the Examiner, since Kamarei teaches applying the freeze-thawing and freeze-drying steps recited in claim 27 to prepare lipoproteins and Proksch teaches measuring the amount of lipoprotein, the other step recited in claim 27, the combination of these two references renders claim 27 obvious.

Applicants disagree that Proksch teaches a method of measuring the amount of lipoprotein in a lipoprotein standard, as required by claim 27. Proksch is concerned with preparing lipoprotein diluents useful for standards and references for **cholesterol** and/or **triglyceride** assays. More specifically, this reference teaches determining the amounts of **cholesterol** and **triglyceride** in a lipoprotein diluent. As **cholesterol** and **triglyceride** are lipids, **not lipoproteins**, Proksch clearly does not teach or suggest a step of determining an amount of lipoprotein in a lipoprotein standard. Differently, claim 27 requires determining an amount of the denatured lipoproteins in a lipoprotein standard. According to the specification:

> The method for determining the denatured lipoprotein in the fifth aspect described above dose not need to be particularly restricted but may be selected from among the methods which have been heretofore known as useful for the purpose. As concrete examples of the method, such methods as radioimmunoassay (RIA), enzyme immunoassay (ELISA), fluoroimmunoassay (FIA), luminescent immunoassay, agglutination immunoassay, immynoephelometry, and nephelometric immunoassay which are immunogic determination of denatured lipoprotein contained in a blood component by causing a given sample to **contact the lipoprotein to an antibody capable of recognizing the denatured lipoprotein and measuring the reactivity of the antibody** with the sample may be cited. See page 25, lines 17-30, emphasis added.

Clearly, claim 27 requires determining an amount of lipoprotein, but not lipid, in a lipoprotein standard.

Kamarei also does not teach or suggest the step of determining an amount of the lipoprotein in a lipoprotein standard, as acknowledged by the Examiner. See the Office Action, page 4, third paragraph.

In view of the above remarks, Applicants submit that Kamarei and Proksch, in combination, do not render claim 27 obvious. They also do not render obvious claims 29, 58, 59, and 62-64, all of which depend from claim 27.

Applicants further rebut below this obviousness rejection on a separate and independent ground. More specifically, the Examiner has erred in concluding that Kamarei teaches performing freeze-thawing and freeze-drying in combination.

Kamarei states that

> [v]arious methods may be used to prepare the material used in the extraction process, including, but not limited to grinding, crushing, comminuting, high and low pressure pressing, cryogrinding, flaking, sonication, freezing, freeze-thaw treatment, freeze-drying, emulsification, homogenization, filtration, high speed mix, centrifugation, cell separation, mechanical separation, thermal treatment, and other physical treatments; chemical treatment such as treatment with inorganic and organic acids, bases, solvents, surface active agents, colorants, ionization radiation treatment; enzymatic treatment such as endogenous and/or exogenous enzymatic treatment, and any combination of more than one of the above methods of treating sample. See column 8, lines 39-52.

In other words, it discloses as many as **26** methods and their random combinations that can be used to prepare tissue samples ready for supercritical fluid extraction. In view of the just-quoted statement from Kamarei, the Examiner asserts that

> [w]hile the reference (Kamarei) itself is directed towards a supercritical fluid extraction process, the reference sufficiently discloses teaching of steps that anticipate [render obvious] the instant claims [excluding the last step claim 27]. For example, the combination of the freeze-thaw and freeze-drying processes would necessarily have to be performed in the order of (1) freeze-thaw and then (2) freeze-drying (i.e., freezing and melting a solution containing lipoprotein; freeze-drying the melted solution), since the opposite order produces dried material that lacks water in order to perform the thawing process. See the Office Action, page 3, third paragraph.

Applicants respectfully disagree. "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." See MPEP 2143.01. Neither Kamarei nor Proksch teaches or suggests combining freeze-thawing and freeze-drying to prepare a denatured lipoprotein standard, as required by claim 27.

The Examiner clearly relies on impermissible hindsight to reach his conclusion of obviousness. The law has well settled that "[o]ne cannot use hindsight reconstruction to **pick and choose** among isolated disclosure in the prior art to deprecate the claimed invention." See, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988, emphasis added). In this case, Kamarei simply provides a laundry list including as many as 26 methods and states that **any combination of more than one** of these **26** methods can be used to prepare tissues ready for the extraction process. Of note, there are

$$P_{26}^{2} = \frac{26!}{(26-2)!} = 26x25 = 650$$

combinations including two ordered methods chosen from the listed 26 methods.[1] Stating "**any combination of more than one method**," Kamarei clearly suggests combinations of 2 to 26 methods. As the respective numbers of combinations of three and more methods are all much higher than 650, Kamarei actually discloses myriad combinations based on the 26 listed methods, without particularly pointing out the combination of freeze-thawing and freeze-drying. Thus, all the Examiner has done here is, with the benefit of the knowledge of claim 27, **picking and choosing** one combination, i.e., freeze-thawing and freeze-drying, out of the myriad combinations suggested in Kamarei. As the law prohibits this hindsight approach, Applicants submit that, on

[1] The Examiner asserts in the just-quoted paragraph that the freeze-thawing step must be performed before the freeze-drying step. Applicants disagree. Indeed, it is possible to perform these two steps in a reverse order, e.g., freeze-drying a solution, dissolving the powder thus obtained in a solvent, and then freeze-thawing the resultant solution. Note that claim 27 requires performing freeze-thawing and freeze-drying in this order. Applicants thus consider the order of performing two methods in calculating the number of possible combinations of two methods chosen from the 26 methods listed in Kamarei.

this second ground, the Examiner clearly erred in relying on Kamarei, together with Proksch, to reject claim 27 for obviousness.

Even if a skilled person in the art had picked and chosen freeze-thawing and freeze-drying according to Kamarei, modifying this reference in view of Proksch would not have afforded the method of claim 27. As pointed out above, neither reference teaches or suggests the step of determining the amount of the denatured lipoprotein in a lipoprotein standard, as required by claim 27. See discussion at page 9, line 26 through page 10.

In view of the above remarks, Applicants submit that the combination of Kamarei and Proksch does not render claim 27 obvious. Nor does it render obvious claims 29, 58, 59, and 62-24, all of which depend from claim 27.

Rejection over Magneson in view of Proksch

Claims 27, 29, 58-60, and 62-64 stand rejected as being obvious over Magneson, US Patent 5,547,873 ("Magneson") in view of Proksch. See the Office Action, pages 5-6, section 6. Applicants have cancelled claim 60.

Megneson teaches a method for preparing a composition for stabilizing proteins for long term dry storage and for recovering their native structures. Proksch has been discussed above.

Megneson, like Proksch, does not teach or suggest the step of determining the amount of denatured lipoprotein in a lipoprotein standard, as required by claim 27. For the same reasons set forth above at page 9, line 25 through page 10, last line, Applicants submit that the combination of Megneson and Proksch does not render these claims obvious.

Applicants now address the Examiner's ground for rejection. More specifically, Applicants disagree with the Examiner's position that Megneson teaches a method including exactly the same steps (excluding the last step) recited in claim 27.

The Examiner asserts:

> "[b]ecause Magneson describes a method with **exactly the same steps** [excluding the last step of claim 27, i.e., determining the lipoprotein amount taught in Proskch] as the claimed invention, one of ordinary skill in the art following the disclosed steps would necessarily perform the claimed

> invention and arrive at the **same end result**." See the Office Action, page 7, third paragraph, emphases original.

As discussed below, Applicants respectfully disagree that the claimed invention includes **exactly the same steps** of the Magneson method and that they arrive at the **same end result**.

Claim 27, the only independent claim, covers a method of producing a **denatured** lipoprotein standard. Indeed, the term "denatured lipoprotein," recited in both the preamble and body of claim 27, is clearly a limitation of this claim. In contrast, Magneson teaches a method of stabilizing proteins so that they can be recovered in their **native structures**. More specifically, Magneson states:

> This invention relates to a blood plasma or plasma-derived composition containing lipoproteins and other cardiovascular markers in a quality control material, which has been stabilized for long term dry storage and to recover essentially all of their **native protein structural determinants** ... In particular, this invention pertains to a freeze dry lyophilized human serum-based calibrator/control material that stabilize its endogenous and exogenous lipoprotein and cardiovascular proteins' **structural integrity** for long term shelf life." See column 2, lines 9-19; emphases added.

Thus, a person of ordinary skill in the art would have known that performing the Magneson method, modified in view of Prosksh, would arrive at an end result different from that of performing the claimed method, i.e., **native lipoprotein** vs. **denatured lipoprotein**. As different end results are achieved by the method of claim 27 (excluding the last step) and the Magneson method, a skilled artisan would have readily recognized that the Magneson method would not include exactly the same steps as the claimed method (excluding the last step). Indeed, the Magneson method includes a defibrinating step and a diafiltering/dialyzing step (see column 3, lines 12-21, and column 4, lines 33-42), which are not required by the method of claim 27.

For the reasons set forth above, Applicants submit that the combination of Magneson and Proskch, does not render claim 27 obvious. It also does not render obvious claims 29, 58, 59, and 62-64, which all depend from claim 27.

CONCLUSION

In view of the above remarks, Applicants submit that claims 27, 29, 58, 59, and 62-64 are not obvious over Kamarei or Megnson, in view of Proskch. Thus, allowance of these claims is respectfully solicited.

Enclosed is a $ 450 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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